(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 January 2005 (20.01.2005)

PCT

(10) International Publication Number
WO 2005/005384 A1

(51) International Patent Classification[7]: C07D 207/34

(21) International Application Number:
PCT/TR2003/000062

(22) International Filing Date: 15 July 2003 (15.07.2003)

(25) Filing Language: English

(26) Publication Language: English

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

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— *of inventorship (Rule 4.17(iv)) for US only*

Published:

— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR THE PREPARATION OF AMORTPHOUS ATORVASTATIN CALCIUM WITHOUT INTERCONVERSION OF ANY CRYSTALLINE FORM

(57) Abstract: The invention relates to a novel process for the preparation of amorphous atorvastatin calcium salt (2:1) from atorvastatin tert-butyl ester (Figure 1). The preparation comprises: (a) dissolving atorvastatin tert-butyl ester (Figure 1) in a solvent, (b) adding an aqueous alkaline or alkaline earth metal hydroxide solution, (c) removing of the solvent, b) adding water and a water non soluble solvent, e) adding an aqueous calcium salt solution, f) separation of the phases and removing of the solvent to obtain desired amorphous atorvastatin calcium and hydrates thereof. The process disclosed herein gives amorphous form directly without interconversion of any crystalline form into amorphous form.

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PROCESS FOR THE PREPARATION OF AMORPHOUS ATORVASTATIN CALCIUM WITHOUT INTERCONVERSION OF ANY CRYSTALLINE FORM

The accompanying drawings show as follows:

Fig.1 shows the formula of [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-tert-butylheptanoate.

Fig.2 shows the formula of [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Atorvastatin calcium).

Fig.3 demonstrates the X-Ray diffractogram of amorphous form of atorvastatin calcium wherein the horizantal axis presents 2θ and the vertical axis corresponds to peak intensity.

Atorvastatin calcium, the substance known by the chemical name [R-(R*, R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt is a synthetic HMGA-CoA reductase inhibitor which is used for the treatment of hyperlipidemia and hypercholesterolemia. Atorvastatin in the pharmaceutical compositions is usually prepared as its calcium salt since it enables atorvastatin to be conveniently formulated in the pharmaceutical formulations.

Process for the preparation of atorvastatin and key intermediates are disclosed in the US patent numbers: 5,003,080; 5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,155,251; 5,216,174; 5,245,047; 5,248,793; 5,280,126; 5,342,952; 5,397,792. All these process give mixtures of crystalline and amorphous forms with unsuitable filtration and drying characteristics rendering them unsuitable for large scale production. Atorvastatin calcium can exist in an amorphous form or in one of the crystalline forms, which are disclosed in the patent applications WO 97/3958, WO

97/3959, WO 97/3960. These studies provided more favorable filtration and drying characteristics.

Atorvastatin calcium is the substance which is sparingly soluble in water, with pKa 4,5 and it has been found that the crystalline forms are less soluble than the amorphous form, which may cause problems in bioavailabilty of atorvastatin in the body. It is very important to ensure uniformity of the substance being employed in a pharmaceutical formulation.

There are basically two different known routes in the literature to prepare amorphous atorvastatin calcium;

(1) from the crystalline form of atorvastatin calcium, which comprise:

dissolving crystalline form of atorvastatin in a solvent and removing of solvent (US 6,087,511) or alternatively adding a non solvent and filtering the precipitated amorphous form (WO 97/03960, US 6,274,740, US 6,087,311, US 6,528,660).

(2) from a reaction mixture of an intermediate of atorvastatin calcium, which comprise:

(2i) hydrolysis of atorvastatin lactone and having atorvastatin calcium in a solvent such as halogenated hydrocarbons, aliphatic esters or aromatic hydrocarbon, adding an anti-solvent such as ether or non-polar hydrocarbons and filtering the desired amorphous atorvastatin calcium (WO 03/018547).

(2ii) A similar process is described in the 2i (WO03/018547), but the amorphous form is obtained from aqueous phase by filtration (WO02/083637, WO02/083638, WO02/059087).

We report here a process for the preparation of the amorphous atorvastatin calcium and hydrates thus consist of:

a) dissolving atorvastatin tert-butyl ester (Figure 1) in a solvent,
b) adding an aqueous alkaline or alkaline earth metal hydroxide solution to the reaction mixture,
c) removing of the solvent,
d) adding water and a water non soluble solvent,
e) adding an aqueous calcium salt solution to the reaction mixture,
f) separation of the phases and removing of the solvent to obtain desired amorphous atorvastatin calcium and hydrates thereof.

The process disclosed herein gives amorphous form of atorvastatin calcium in a simple process without interconversion of any crystalline form. Additional solvents are not necessary to precipitate amorphous form. Additionally to these, the problem of removal of water from the product is not observed.

EXAMPLE

5 g of atorvastatin tert-butyl ester (Fig.1) was dissolved in 100 ml of methanol, and a solution of 0.390 g of NaOH / 15 ml of water was added. Reaction mixture was stirred for 1 h at 50^0C. After 1 h, TLC showed no starting material (TLC was performed on silica plate, eluent: Hexane/ethyl acetate: 1/1). Methanol was removed under reduced pressure. 100 ml of water and 100 ml of ethyl acetate were added. A solution of 0.870 g of $Ca(CH_3COO)_2$. X H_2O / 20 ml of water was added. Reaction mixture was stirred for 1 h at 50^0C. Mixture was cooled to room temperature and the phases were seperated. The organic phase was washed with 2X50 ml of water. The organic phase was concentrated under vacuo at 50 ^{0}C to give desired amorphous atorvastatin calcium.

CLAIMS

1. An improved process for the preparation of amorphous atorvastatin calcium, having formula of Figure 2 which comprises;

i) dissolving atorvastatin tert-butyl ester having formula of Figure 1 in a solvent,

ii) adding an aqueous solution of alkaline or alkaline earth metal hydroxide,

iii) removing of the solvent,

iv) adding water and a water non soluble solvent,

v) adding an aqueous solution of a calcium salt,

vi) separation of the phases and removing of the solvent to obtain desired amorphous atorvastatin calcium and hydrates thereof.

2. The process of Claim 1i, wherein solvent is methanol.
3. The process of Claim 1ii wherein alkaline or alkaline earth metal hydroxide is sodium hydroxide.
4. The process of Claim 1iv wherein the solvent is ethyl acetate,
5. The process of Claim 1v wherein calcium salt is, calcium acetate.

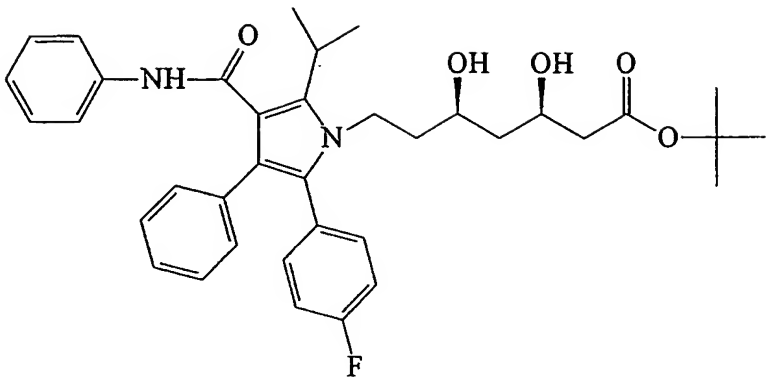

Figure 1.

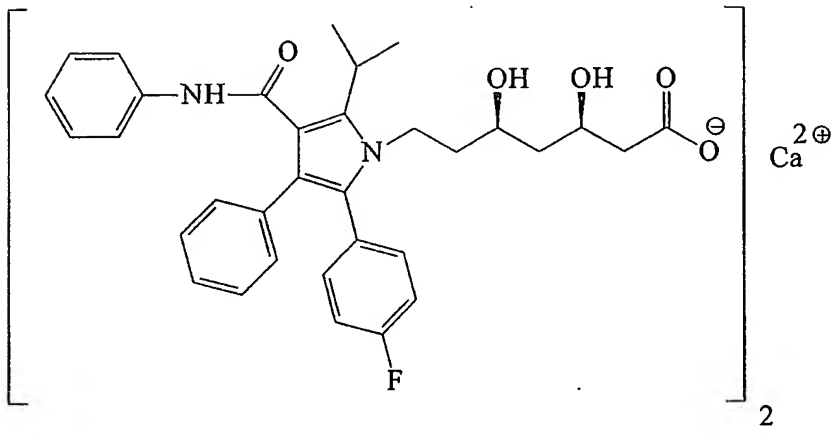

Figure 2.

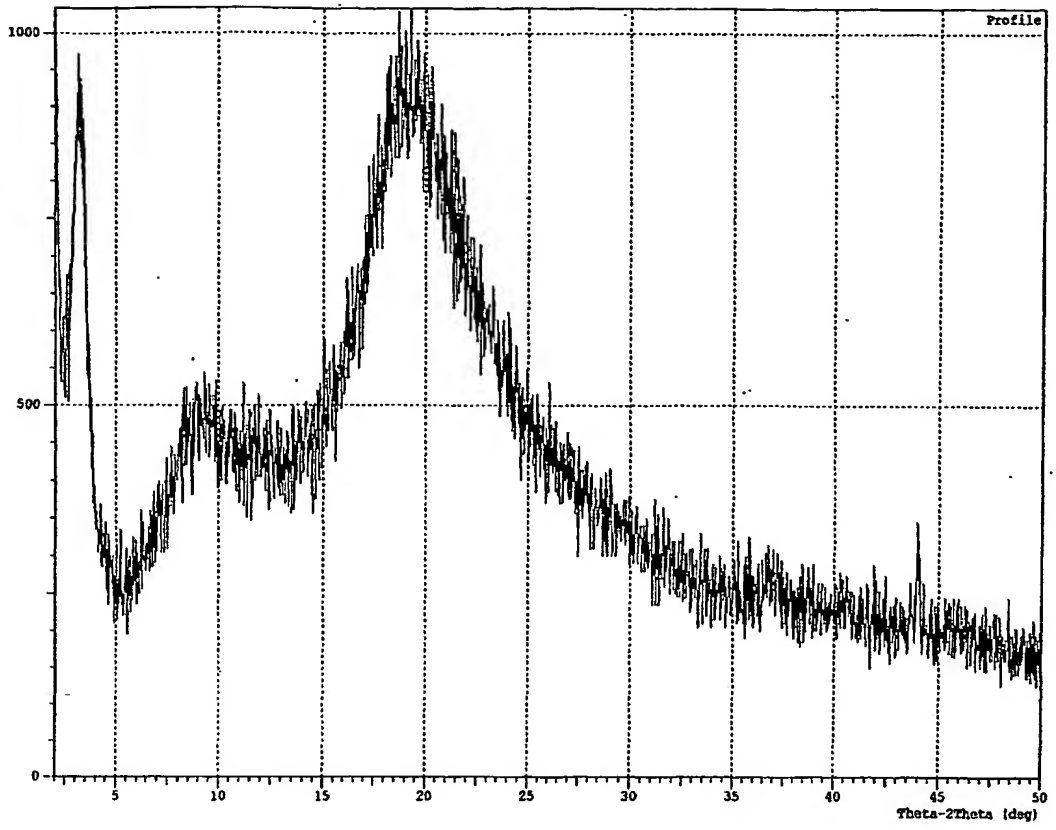

Figure 3.

INTERNATIONAL SEARCH REPORT

Inte ıal Application No
PCT/TR 03/00062

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D207/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/059087 A (LEK TOVARNA FARMACEVTSKIH ; SORSAK GORAZD (SL)) 1 August 2002 (2002-08-01) cited in the application page 6, line 18 - page 9, line 14; claim 1	1-5
Y	BAUMANN K L ET AL: "THE CONVERGENT SYNTHESIS OF CI-981, AN OPTICALLY ACTIVE, HIGHLY POTENT, TISSUE SELECTIVE INHIBITOR OF HMG-COA REDUCTASE" 21 April 1992 (1992-04-21), TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, PAGE(S) 2283-2284 , XP000608147 ISSN: 0040-4039 page 2284, line 1 - line 10	1-5

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
13 February 2004	19/02/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Von Daacke, A

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/TR 03/00062

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/083637 A (CADILA HEALTHCARE LTD ; PANDITA KANWAL (IN); AGARWAL VIRENDRA KUMAR (I) 24 October 2002 (2002-10-24) cited in the application page 5, line 1 - page 8, line 25; claim 1	1-5
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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